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Toward the Twenty-First Century: Lessons from Lead and Lessons Yet To Learn

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A consideration of recent research on lead is instructive for developing research strategies in environmental toxicology. Lead research has demonstrated fruitful interactions between clinical and basic science. Thus, while epidemiological studies have suggested that central nervous system (CNS) effects in children are observed at the lowest increments of lead exposure, basic research has elucidated some of the molecular events that underly this lack of threshold at the neuronal level. Similarly, clinical studies indicate that early exposure to lead produces functionally irreversible damage to the CNS; experimental research demonstrates that this irreversibility may involve failure to remove lead from brain, permanent effects on synaptogenesis; and chelant-induced redistribution of lead from the periphery to the CNS. Lead toxicokinetics demand reevaluation. New data on release of bone stores of lead during physiological conditions of demineralization indicate that mobilization of bone lead adds to *in utero* exposure of the fetus. Furthermore, postmenopausal demineralization of bone can increase blood lead levels in women by 25%; this raises concern about the potential effects of lead in an aging population and the difficulties in comprehensive exposure assessment.

Introduction

There is considerable merit, but also some shame, to basing a discussion of subtle effects of environmental agents on human health in the context of our end-of-the-century knowledge of lead poisoning. The merit lies in the advances of basic and clinical research during the last two decades that amply demonstrate the progress made in considering an important disease entity in its less overt, subclinical, subtle, and finally mechanistic terms. The shame arises from realizing that we are grounding this discussion with its implications for the future of toxicology and environmental health in considering a poison having human health effects that have been recognized, varyingly since the second century B.C.

The premise of this paper is that the elucidation of the low-level effects of lead has been a source of important and far-reaching answers to critical questions such as the reversibility and the dose response for these effects. This progress has equally used the results of clinical, epidemiological, and basic research. Basic research has provided the mechanistic information that is used to base hypotheses for the relationship between dose and effect for lead at low dose and for predicting the potential reversibility of these low-level effects when exposure is reduced.

Dose Response

From the seminal epidemiological studies by Needleman et al. (*1*), now replicated by many other investigators around the world, data have been derived that are consistent with a hypothesis that the deficits observed in young children with increased lead absorption are without threshold. That is, in the comprehensive behavioral evaluations done by Needleman and Yule (*2*), the relationship between dentine lead, a marker of cumulative lead dose, and increased incidence of problem behaviors seemed smooth, from the lowest concentrations of lead in teeth through the highest. This suggestion of a lack of a detectable threshold was strengthened by the data from England (*3*), where, for a variety of reasons, lead exposure is generally lower. The children in the English studies could be combined with those in the U.S. studies to extend the overall dose-response curve lower, as Needleman and others have done with meta-analysis (*1*).

In discussions of threshold, which frequently become theoretical rather than empirical, as Patterson has pointed out, no population in this era can be considered true controls for lead because all post industrial humans have greatly increased body burdens of lead, as compared to pre-industrial populations (*4*). Thus, while theoretically there may be a threshold for the biological effects of lead (if absolutely lead-free systems could be compared to those with very low-level exposures) in the context of generalized lead contamination and even of experimental systems such as cell cultures, it is more relevant to determine whether or not there are nonmonotonic regions of the empirical dose-response curve between controls and exposed populations or systems.

In such circumstances, even with the general exposure of so-called controls, it is still possible to observe

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and to rationalize thresholds for end points in lead toxicity. In a recent analysis of data by Schwartz et al. (*5*) on peripheral neurotoxicity in children exposed to lead, we found that the available data on nerve conduction velocity are best fit by a quadratic, nonlinear function, suggesting that a threshold may exist for this toxic effect (*5*). This threshold may result from the mechanisms involved in neurotoxicity, such as the need to recruit several nerve fibers into a dysfunctional state in order to produce biologically significant or detectable decrements in compound nerve action potentials. Conversely, for central nervous system (CNS) toxicity, this threshold does not appear to occur.

When considering how lead could produce neurotoxic effects in the CNS with no empirically observable threshold, the most likely candidate for such a mechanism is the ionic nature of lead as a neurotoxin. The hypothesis that lead might interfere with ions that are essential to supporting chemical neurotransmission is based on experimental studies using different neuronal preparations. At the neuromuscular junction, there are clear lead/calcium interactions that are consistent with an antagonism between the two cations in the regulation of stimulation-dependent transmitter release. However, the unstimulated miniature endplate potentials (MEPPs) release of neurotransmitter at peripheral cholinergic junctions was actually increased by lead. These findings indicated that the interactions between lead and calcium were likely to be complex (*6*).

In the central nervous system, *in vitro* lead exposure to brain cells (neurons and capillary epithelial cells) resulted in increased transmembrane calcium influx. In synaptosomes, which are pinched off nerve terminals prepared from rat brain, this increased influx of calcium appeared to reflect altered calcium fluxes at the level of mitochondria (*6,7*). When synaptosomes were prepared as ghosts (resealed membranes), the lead-induced increase in transmembrane calcium influx was abolished (Table 1) (*8*). A similar conclusion was reached by Pounds (*9*) studying hepatocytes in culture. Pounds stated that lead affected a deep compartment of calcium regulation that was probably mitochondrial, and it caused an overall increase in the uptake of calcium by these cells, particularly under conditions that stimulated their activity (e.g., insulin).

Table 1. ^{45}Ca uptake and binding by synaptosomes, membranes, and synaptosomal ghosts.

	^{45}Ca bound, ng-atoms/mg protein/4 min[a]				
	Lead concentration				
Fraction	0	10^{-8}	10^{-7}	10^{-6}	10^{-5}
Synatosomes	65.0	72.3	80.9*	89.1*	145.2*
Synaptic membranes	5.1	4.9	5.6	8.2	3.0
Synaptosomal ghosts	6.6	5.8	5.4	7.8	4.5

[a]Aliquots of fractions were incubated for 4 min at 37°C with Pb and $^{45}CaCl_2$ (2–7 × 10^5 cpm). Results are means for six experiments, each done in triplicate.

*Significantly different from [Pb] = 0, $p < 0.05$.

Figure 1 shows schematically how a mitochondrial mechanism might result in altered transmitter release. As confirmed by X-ray microprobe analysis, nerve terminals preferentially sequester lead in mitochondria. These lead-exposed mitochondria also contain, qualitatively, more calcium than do control synaptosomes (*10*). Lead-containing mitochondria are refractory to the action of sodium to promote the efflux of bound calcium into the cytosol. The sodium-dependent release of mitochondrially bound calcium is a major intracellular mechanism for regulating the concentration of cytosolic free [Ca^{2+}] in excitable cells. The release of stored calcium, by sodium, one of the ionic carriers of altered membrane potential, acts to decrease the voltage-dependent influx of calcium that follows membrane depolarization in nerve cells (*7*). By decreasing this intracellular release of stored calcium, the transmembrane gradient for calcium remains high, and relatively more calcium enters the cell when membrane pores are open. This transmembrane flux of calcium appears to be critical for depolarization-coupled transmitter release.

These effects appear to involve molecular interactions

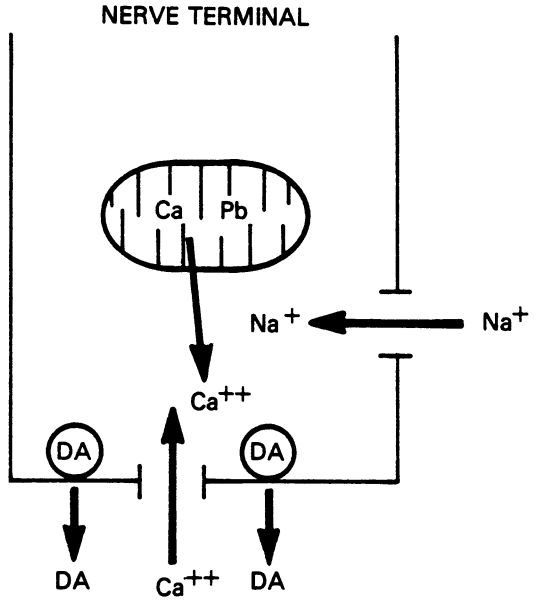

FIGURE 1. Schematic represention of the mechanism of action of lead to alter sodium-calcium interactions resulting in increased release of vesicle-bound transmitter. Lead is stored in mitochondria, in proximity to Ca^{2+} (possibly at the same site, a Ca^{2+}/Mg^{2+} ATP). In this molecular complex, Ca^{2+} is less releasable on voltage-dependent increases in intracellular Na^+ (shown entering the cell through a sodium pore). As a consequence, concentrations of free Ca^{2+} in the cytosol are unbuffered by mitochondrial Ca^{2+}, and the transmembrane gradient for Ca^{2+} is augmented. This results in increased influx of Ca^{2+} across the membrane under conditions where Ca^{2+} channels are opened (depolarization); the influx of Ca^{2+} is associated with increased rates of vesicle adhesion to the presynaptic membrane-active zone as well as increased rates of vesicular exocytosis. See Silbergeld and Adler (*1*) for details.

among lead, calcium, and sodium. Although the exact stoichiometry among these ions at the critical site (probably an ATPase in mitochondria) (*8*) is not yet known, it is plausible to hypothesize that it is on a mole-for-mole basis. Thus mechanistically, the basic research about lead supports the strong indications in epidemiological literature that low-level lead exposure is practically without a threshold (over the ranges that are currently encountered.)

Interest in lead-calcium interactions is not restricted to neurotoxicity, although this has been the major area of interest. With the finding that low-level lead exposure may also affect growth and stature (*11*) there is growing concern about the effects of lead on calcium status related to bone. Recent experimental studies on bone cells in culture confirm that bone cell calcium metabolism is also affected by lead at low concentrations (*12*). This is a subject which will be discussed further, but the lessons of lead-calcium interactions in ionic mechanisms of neurotransmission may be useful to keep in mind while these new areas of calcium-dependent lead toxicity are explored.

Mechanisms of Irreversibility

In evaluating the significance of relatively low-level lead exposure, the potential for reversing these effects is of major concern, particularly in young children exposed prenatally or postnatally. Early detection and intervention might alter the course of dysfunction for these children. This has been explored in mechanistic as well as descriptive experiments. Descriptively, there are a number of studies that have found persistent neurotoxic effects in animal models. However, the nature of these effects and the neurochemical substrate for them are important components to understanding reversibility.

Early clinical descriptions of the consequences of lead exposure in young children referred to a certain constellation of neurobehavioral disorders with varying components of what has been called minimal brain dysfunction (MBD), attention deficit disorder (ADD), or hyperactivity. While, at times, there has perhaps been overemphasis on exact homologies between the relatively undefined clinical entity and models produced in animals, the concept has been useful in suggesting critical experiments.

A monoaminergic hypothesis has been proposed for many of the symptoms of MBD/ADD (*13*). The clinical use of the stimulants methylphenidate and *d*-amphetamine has also been cited as a basis for this biochemical hypothesis: basically, that monoaminergic systems are dysfunctional in these children (*14*). Although critical tests of this hypothesis have been inconclusive (largely because of barriers to detecting the status of chemical neurotransmission in the brain without invasive techniques), this hypothesis is consistent with the larger aminergic hypothesis of mental dysfunction and major affective disorders.

The demonstration that lead-exposed rodents, hyperactive or not, had abnormal dose-response curves for stimulants (*15,16*) provoked considerable exporation of monoaminergic function in lead-exposed animals.

As summarized by Winder and Kitchen (*17*), these studies have not been entirely consistent. However, the preponderance of recent studies have found evidence for the increased release of dopamine in lead-exposed animals (decreased levels of transmitter, increased turnover, increased concentrations of metabolites). While these effects probably do not explain all the clinical findings associated with low-level lead exposure, they have provided a potential marker for lead neurotoxicity.

As shown in Figure 2, we have explored the functional status of monoaminergic function in lead-exposed children by measuring urinary metabolites collected in quantitative 24-hr urine samples (*18,19*). Both homovanillic acid (HVA) and vanillylmandelic acid (VMA) were measured by standard fluorometric techniques. However, VMA appeared to be less stable; thus our analyses have focused on HVA. Increased levels of HVA were associated with increased blood lead in these children and had statistical significance. The association of this biochemical marker with neurologic status or other indices of lead toxicity is not known. However, this effect appears independent of lead activity on heme synthesis, because there was very poor correlation between HVA and urinary aminolevulinic acid (ALA), or erythrocyte protoporphyrin—two markers of heme synthesis used to diagnose lead exposure (*19*). Levels of urinary HVA were also studied in a group of children who underwent chelation therapy for excessive lead

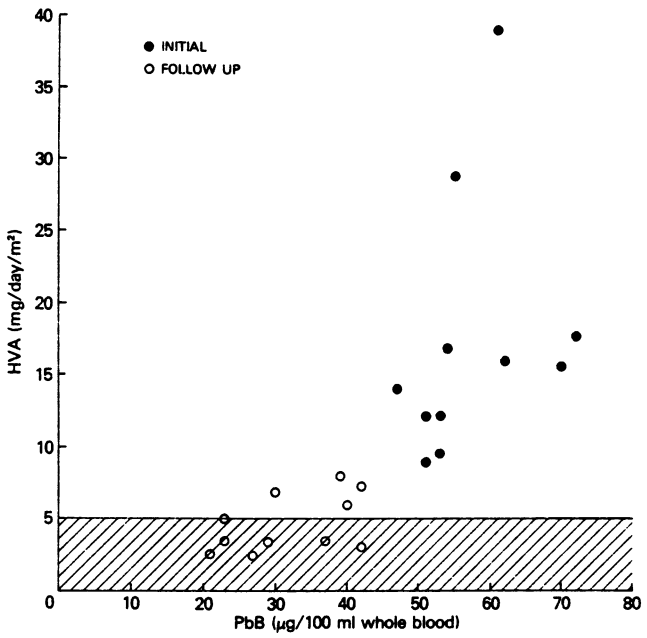

FIGURE 2. Blood lead (PbB) levels and urinary homovanillic acid (HVA) in 11 children, measured before (solid circles) and after (open circles) chelation therapy. The shaded area indicates the range of control values for urinary HVA in children. See Chisolm and Silbergeld (*19*) for details.

exposure. This treatment was effective at lowering blood lead levels, as shown in Figure 2. Also, levels of HVA were also reduced in the children after treatment. However, it is important to note that even with extensive chelation (EDTA and penicillamine) and extensive excretion of lead in urine, monitored over treatment, the levels of urinary HVA in many of these children still remained elevated, when compared to controls (Chisolm and Silbergeld, unpublished data).

The elevated urinary HVA may reflect any of the following phenomena: first, chelation was unsuccessful at lowering concentrations of lead in the brain; second, that the lead-induced damage to catecholaminergic neurochemistry was not reversed by removing lead; and third, that chelation actually increased brain lead exposure, at least in the relatively short-term period following therapy by transferring lead from bone and peripheral soft tissue stores back to the blood and recirculating it to the brain.

Experimental evidence suggests that chelation using EDTA is not particularly effective at lowering brain lead concentrations. Therefore, the simplest explanation of the observed persistence of elevated urinary HVA may be correct, that lead remains *in situ* to alter the metabolism of dopamine. The second alternative may also be correct. If lead exposure occurred during critical periods of synaptogenesis and chemical linkages within neural networks, then early exposure might result in fixed damage. The third hypothesis that treatment might exacerbate lead neurotoxicity is being explored at the present time. Our studies *in vitro* found that the addition of a powerful sulfhydryl chelator, dithiothreitol, could prevent lead effects only when added before lead, not after (*7*). This also suggested that intraorgan and intracellular lead is difficult to remove. The slow turnover of brain components results in the relative fixation of lead at the target site long after external sources are reduced.

In summary, the aminergic hypothesis has been useful for experimental research on the neurochemical basis of lead toxicity. Moreover, the involvement of this system is, at least, broadly consistent with some of the features of neurobehavioral pathology described in clinical populations. And finally, the hypothesis that lead-induced deficits might not be reversible may involve poorly reversible lesions of catecholaminergic pathways in the brain. These irreversible deficits are most clearly shown in some of the newer long-term prospective studies of children exposed originally *in utero*.

Alternative Mechanisms for Lead Neurotoxicity

It is well known that lead is a potent disrupter of heme synthesis (*20*). Lead acts to inhibit the rate-limiting enzyme ALA dehydrase (ALAD), and probably also reduces activity of heme oxygenase and ferrochelatase. Because of the feedback mechanisms in this pathway, lead-induced inhibition of ALAD is associated with depression and overactivity of ALA synthase (ALAS) and porphobilinogen (PBG) deaminase. As a consequence, levels of ALA and PBG greatly increase in lead-exposed persons.

The role of these biochemical effects in lead toxicity is not known. As shown in Figure 3, it can be hypothesized that depleting critical stores of heme might affect a wide range of enzyme and cytochrome systems. Moreover, the overproduction of ALA and PBG might itself create toxic effects if these two molecules are themselves bioactive. The analyses of neurotoxicity in workers exposed to lead, which incorporate markers of heme synthesis, provide further explanation of the dose-relatedness of these effects over and above that conferred by correlations based on blood lead levels alone. Two recent reviews have examined how lead-included alterations in heme synthesis might result in neurotoxic signs and symptoms (*22,23*): lead may deplete heme for critical oxidative pathways including cytochromes that carry intracellular oxygen; altered heme synthesis may deprive glia of critical components and result in the failure of normal neuronal-glial interactions involved in the supply of precursors for neurotransmitters; altered heme synthesis may have an impact on two amino acids known to be involved in neurotransmission, glycine (the precursor to ALA) and serotonin (*24*); and certain heme precursors that accumulate in abnormally high concentrations may be neurotoxic. Considerable attention

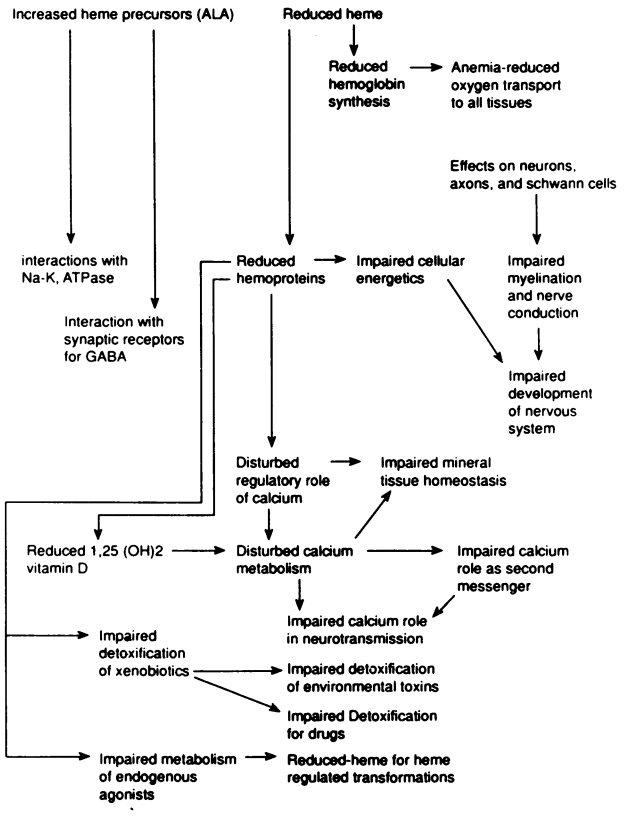

FIGURE 3. Summary of biological effects of lead associated with altered heme synthesis.

has been given to the biological activity of ALA, which structurally resembles γ-aminobutyric acid (GABA) and has been shown to displace GABA from synaptic membrane receptors (*22*). Recently, it has been proposed that PBG may displace benzodiazepines from mitochondrial membrane receptors in peripheral organs (*25*). It is also of interest to examine the structure of PBG and compare it to other pyrrole and pyrrolelike structures. Of particular interest is the similarity between PBG and the well-known neurotoxin kainic acid (*26*). We attempted to inject PBG into the basal ganglia of rats to determine if it has excitotoxin-like activities; however, to date, we are not certain that we have been able to adequately solubilize or protect this molecule in order to deliver a relevant pharmacological dose to potentially sensitive cells (Schwartz and Silbergeld, unpublished observation).

Consideration of the possible mechanistic role of altered heme synthesis in lead toxicity is important for two reasons: first, there is evidence (*27*) for genetic heterogeneity in the sensitivity of a critical enzymic target for lead in this pathway, ALAD, which may confer interindividual differences in susceptibility; second, alterations in heme synthesis are an outcome of many other chemical exposures, notably the halogenated hydrocarbons; like lead, some of these hydrocarbons have figured in episodes of significant human exposure and alleged health effects. The establishment of sensitive markers for the early effects of these agents might assist in refining clinical and experimental studies. These markers might also provide bases for mechanistic hypotheses for actions, thresholds, and reversibility questions similar to those that have arisen with lead.

Newer Thoughts on Reversibility: Lead Toxicokinetics

The apparent irreversibility of lead toxicity, which has been reported in two of the long-term prospective studies in children, may result from one of two mechanisms: failure of affected systems to recover (fixed, noncompensible damage), or the persistent presence of lead at the target site. Either mechanism would indicate that lead toxicity is poorly treatable and best prevented.

In addition, the long-term toxicokinetics of lead are only beginning to be examined. It is well known that most of the absorbed lead is stored in bone, which has a long turnover rate and eventually contains about 95% of the body burden of lead. In general, little attention has been paid to this compartment or to the storage of lead. It is considered to be a sequestration or removal of lead from active sites in soft tissues. This may not be true. The kinetics of bone lead may add to the reversibility problem for lead-exposed persons by providing a cumulative store that may release its contents under certain stresses or physiological changes. Data in humans is only beginning to be examined. Studies of lead kinetics in pregnant women are contradictory and confounded by the complexity of compartments for analysis (*28*). Barltrop's pioneering studies suggest that maternal lead stores are released over pregnancy, accounting for the dramatic increases in bone and soft tissue lead concentrations in the fetus over gestation.

We have examined blood lead levels in postmenopausal women, who compose another population where changes in bone physiology occur in response to the hormonal changes associated with loss of reproductive capacity (*29*). In approximately 15% of postmenopausal women, osteoporosis (clinical bone demineralization) occurs, representing a substantial and rapid loss of mineral from bone (*30*). We used the NHANES II dataset (*31*) and examined blood lead in 800 postmenopausal women, both black (126) and white. As shown in Table 2, postmenopausal women had significantly higher blood lead levels than premenopausal women; this increase was significant even when covariates were considered (diet, exercise, smoking, weight). Interestingly, the increase in blood lead was much greater in whites than in blacks, although in terms of absolute value, blood lead levels were as expected higher in black women. Moreover, the data indicated that mobilization of bone lead probably also occurred in this population with pregnancy. That is, in the postmenopausal sample of women who had been pregnant, the postmenopausal increase was less than in those women who had never been pregnant; this was found in both blacks and whites, but again more predominantly in whites. The results thus suggest that bone lead is stored cumulatively, reflecting long-term exposure and deposition. However, stored bone lead can be mobilized and cause rapid changes in internal exposure under fairly standard conditions.

There are several implications of this new aspect of lead toxicokinetics: First, during pregnancy, mobilization of bone lead in the mother probably contributes to *in utero* exposure, along with the mother's concurrent external dose from the environment or her occupation. One lesson is that evaluation of the mother at the time of pregnancy may not be sufficient to predict exposure of the fetus and neonate. Already, one case has been re-

Table 2. Effect of menopause and prior pregnancy on blood and plasma lead levels in women.

	All women		White		Black	
Change in blood lead	mcg/dL	% Change	mcg/dL	% Change	mcg/dL	% Change
Pre/postmenopause	1.47	12.6	1.67	14.7	0.62	4.6%
Pre/postmenopause, never pregnant	2.56	22.0	2.67	23.4	1.31	9.8
Pre/postmenopause, ever pregnant	1.37	11.8	1.45	12.7	0.50	3.7

ported regarding a woman, intoxicated with lead as a child, becoming reintoxicated and giving birth to a baby with very high blood lead as a consequence of this mobilization (*32*).

Second, the results raise questions as to the importance of examining the aging population as a group potentially at risk for lead toxicity, based on accumulated body burden lead being released over a relatively short period of time. (Postmenopausal osteoporosis occurs primarily within the first 5 years postmenses.) The relatively large increase in blood lead that might then occur represents a much greater dose-rate than the increase that may have occurred over the years of low-level exposure to external sources of lead in the general environment. Given new knowledge as to the low-level effects of lead, it is not unreasonable to consider some of the following as potential outcomes of such exposure late in life: increased risk of hypertensive heart disease and renal disease; neurotoxicity, including dementing disorders of the elderly; and osteoporosis itself (*29*). These studies need to be conducted as we continue to follow lead as a toxin of critical environmental significance and public health importance into the twenty-first century.

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